2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of cresols and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for cresols based on toxicological studies and epidemiological investigations.

There are three isomers of cresol: o-cresol, p-cresol, and m-cresol. These are described in detail in Chapter 3. In the following discussion, the effects of o-cresol and p-cresol, which have similar toxicities, are generally described prior to those of m-cresol, which is somewhat less toxic. Occasionally, data were available regarding the effects of cresol mixtures (containing the three isomers in varying proportions) and cresylic acids (technical mixtures containing other substances in addition to the three cresol isomers). These are generally discussed after the individual isomers.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure

levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Studies of the inhalation toxicity of cresols have not been adequately detailed. The exposures involved mixtures of vapors and aerosols that were not characterized sufficiently to estimate exposure levels reliably. Furthermore, methods for evaluating the toxicological end points were not adequately described. Therefore, no LSE table or figure containing levels of significant exposure was constructed for this route. Nevertheless, certain general conclusions can be drawn from the reports regarding the toxic potential of inhaled cresols. These are discussed below.

2.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to cresols.

Cresols may be lethal to animals when inhaled (Campbell 1941; Uzhdavini et al. 1972). The inhalation exposure levels and durations that kill animals have not been reliably documented. Lethality has been reported in mice exposed to approximately 178 mg/m^3 of o-cresol aerosol for an unspecified acute duration, suggesting that the minimal lethal exposure level for cresol aerosols may be less than 178 mg/m^3 (Uzhdavini et al. 1972). For longer-term exposure, the minimal lethal level may exceed 50 mg/m^3, since exposure to this concentration of o-cresol for 1 month had no effect on mouse mortality (Uzhdavini et al. 1972).

2.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, or musculoskeletal effects in humans or animals following inhalation exposure to cresols.

Respiratory Effects. When inhaled as a concentrated aerosol, o-cresol is a respiratory irritant in humans; however, the minimal exposure level and duration associated with irritation have not been reliably documented. Following brief exposures to 6 mg/m^3, 8 out of 10 subjects complained of mucosal irritation symptoms including dryness, nasal constriction, and throat irritation (Uzhdavini et al., 1972).

Signs of respiratory irritation have been reported in animals acutely exposed to cresol vapors and aerosols, although the levels associated with irritation have not been reliably documented (Campbell 1941; Uzhdavini et al. 1972). Mucosal irritation, as shown by parotid gland secretions, occurred in cats during 30-minute exposures to 5-9 mg/m^3 of o-cresol (Uzhdavini et al. 1972). An assortment of respiratory effects, including inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs were seen in animals exposed to 9-50 mg/m^3 of o-cresol 2-6 hours/day for 1 month or more (Uzhdavini et al. 1972).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to cresols.

Heart muscle degeneration was reported in mice exposed to 50 mg/m^3 of o-cresol 2 hours/day for 1 month (Uzhdavini et al. 1972). The cresol was probably given as an aerosol. Exposure levels were not reliably documented.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to cresols.

Fatty degeneration and centrilobular necrosis were observed in the livers of mice that died following acute exposure to o-cresol; the mean lethal concentration was 178 mg/m^3. Exposure to 9 mg/m^3 for 4 months interfered with liver function in rats, as shown by increased susceptibility to hexanol narcosis (Uzhdavini et al. 1972).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to cresols.

Blood was found in the urine of mice acutely exposed to o-cresol; the mean lethal concentration was 178 mg/m^3 (Uzhdavini et al. 1972). Necropsy and histopathologic examination of the mice that died following exposure revealed edema and swelling of the glomeruli, degeneration of the tubular epithelium, and perivascular hemorrhage.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following inhalation exposure to cresols.

Eye irritation was noted in mice briefly exposed to highly concentrated cresylic acid vapors; however, the exact exposure concentrations associated with irritation were not documented (Campbell 1941).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to cresols.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to cresols.

Neurologic effects in animals acutely exposed to cresol aerosols have been reported (Uzhdavini et al. 1972). The effects include mild nervous excitation, muscle twitching accompanied by general fatigue, and clonic convulsions. The exposure concentrations associated with these effects have not been reliably documented; however, they may occur at levels approximating 178 mg/m^3 during a single exposure. Prolonged exposure (2 hours/day for 1 month) to a lower concentration of o-cresol aerosol (50 mg/m^3) reportedly produced degeneration of nerve cells and glial elements in mice (Uzhdavini et al. 1972). The severity of these changes was not discussed, however, and no further details were provided. The exposure concentration associated with this effect was not reliably documented.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to cresols:

2.2.1.5 Developmental Effects
2.2.1.6 Reproductive Effects
2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to cresols.

2.2.2 Oral Exposure

2.2.2.1 Death

Ingestion of cresols can be fatal to humans. Fatalities were described in several case reports involving ingestion of cresol-containing disinfectants. A 37-year-old woman died 4 days after swallowing about 250 mL of a disinfectant described as 50% cresols in a mixture of linseed oil, potassium hydroxide, and water. Death was caused by acute intravascular hemolysis, which resulted in multiple thrombosis and renal failure (Chan et al. 1971). The lethal dose was roughly 2 g/kg of cresols (only about one-half of which was actually absorbed). The same report described the case of a woman who recovered after drinking a smaller amount of the same disinfectant (approximately 100 mL). The urine of both women contained glucuronides of cresol metabolism. A woman who swallowed between 500 and 750 mL of a concentrated cresol mixture died from cardiac arrest after 26 hours (Labram and Gervais 1968). Among the 52 cases of cresol poisoning reported by Isaacs (1922), two patients died, both within 0.5 hours of drinking a disinfectant purported to contain 25%-50% cresols. A woman who drank a disinfectant suspected of containing cresols died 5 days later (Della1 1931). There was little corrosion in the throat so it is probable that not much disinfectant was swallowed. The cause of death was thought to be acute hemorrhagic degeneration of the pancreas, which may or may not have been related to cresol consumption.

There are few reliable studies of the acute lethality of cresols in animals following oral exposure. LD_{50} values (doses lethal to 50% of test animals) in rats were 1,350, 1,800, and 2,020 mg/kg for o-, p-, and m-cresol, respectively (Deichmann and Witherup 1944). Acute LD_{50}, values for various cresylic acid formulations in mice ranged from 500 to 2,050 mg/kg (Campbell 1941). Although LD_{50} values were not determined in other species, minimum lethal values were available for a few species; the small number of animals in these studies, however, limits the reliability of these data. In rabbits, minimum lethal values from ingestion ranged from 620 to 1,400 mg/kg for the three isomers (Deichmann and Witherup 1944). In mink, the minimum lethal value of o-cresol was 200 mg/kg, and in ferrets, it was 400 mg/kg (Hornshaw et al. 1986).

Mortality data were also available for pregnant rats (BRRC 1988a) and rabbits (BRRC 1988b) given cresols repeatedly during gestation in studies of developmental toxicity. Both o- and p-cresol produced mortality among rats given 450 mg/kg/day, whereas m-cresol did not (BRRC 1988a). In rabbits, p-cresol appeared to produce a dose-related increase in mortality at 50-100 mg/kg/day. Rabbit mortality was not affected by exposure to o- or m-cresol (BRRC 1988b).

Exposure to o-, p-, or m-cresol at 450 mg/kg/day produced 12%-60% mortality in adult male and female rats exposed to these compounds in

two-generation reproduction studies. The elevated mortality occurred in both the F_0 and F_1 generation adults (BRRC 1989a, 1989b, 1989c). In 13-week studies of systemic toxicity in rats, elevated mortality resulted only from exposure to o-cresol at 600 mg/kg/day (MBA 1988a); in these studies, p- and m-cresol failed to produce mortality at 450-600 mg/kg/day (1988b, 1988c).

The highest NOAEL values and all reliable LD_{50} and LOAEL values for death in each species and duration category are recorded in Tables 2-la, 2-lb, and 2-1c and plotted in Figures 2-la, 2-lb, and 2-1c.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects of each type in each species and duration category are recorded in Tables 2-la, 2-lb, and 2-1c and plotted in Figures 2-la, 2-lb, and 2-1c.

Respiratory Effects. Diffuse necrosis of the bronchial epithelium was noted in a woman who died after drinking 500-750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was thought to have occurred prior to death. Edema and hemorrhage were also observed, but may have occurred secondary to death. Adhesions and fluid were found in the lungs of a woman who died after drinking a disinfectant suspected of containing cresols (Della, 1931).

Pregnant rats (BRRC 1988b) and rabbits (BRRC 1988a) exposed to o-, p -, and m-cresol were reported to have audible respiration and labored breathing. These effects may be of a neurologic origin, rather than a direct effect on the respiratory system (Section 2.2.2.4). Based on the NOAEL of 5 mg/kg/day for m-cresol for audible respiration in pregnant rabbits (BRRC 1988a), an acute oral MRL of 0.05 mg/kg/day was calculated for this isomer, as described in footnote b in Table 2-1c. Although o- and p-cresol also had NOAEL values of 5 mg/kg/day, MRLs for these isomers were based primarily on more explicit neurological effects and are described in Section 2.2.2.4. Epithelial metaplasia of the trachea has been reported to occur in rats subjected to prolonged exposures to p-cresol (MBA 1988b). Other histopathological changes attributable to oral exposure to cresols in animals have not been reported.

Cardiovascular Effects. A woman who swallowed 500-750 mL of a concentrated cresol mixture exhibited tachycardia with polymorphic ventricular extrasystoles shortly after exposure (Labram and Gervais 1968). This was followed within 26 hours by ventricular fibrillation and cardiac arrest.

In rats exposed to o-cresol (MBA 1988a), p-cresol (MBA 1988b), or m-cresol (MBA 1988c) at levels up to 600 mg/kg/day for 13 weeks, histological examination of the heart revealed no changes that indicated an adverse effect on the heart. Mild increases in relative heart weight (approximately 10%)

TABLE 2-1a. Levels of Significant Exposure to o-Cresol - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	1x				1,350 (LD_{50})	*Deichmann and* Witherup 1944
Systemic								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other	50	175 (decreased body weight gain)		MBA 1988a
3	Rat	(GO)	2 wk 7d/wk 1x/d	Other		600 (decreased food intake)		TRL 1986
4	Rat	(GO)	Gd6-15	Resp	175	450 (audible respiration)		BRRC 1988b
				Hepatic	450			
				Other		450 (decreased body weight gain, food intake)		
5	Rabbit	(GO)	Gd6-18	Resp	5	50 (audible respiration)		BRRC 1988a
				Hepatic	100			
				Derm/oc	5	50 (ocular discharge)		
				Other	100			
Neurological								
6	Rat	(GO)	2 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988a
7	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
8	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
9	Rabbit	(GO)	Gd6-18		5[b]	50 (hypoactivity)		BRRC 1988b

TABLE 2-1a (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
10	Ferret	(G)	1x			200 (incoordination)	300 (unconsciousness)	Hornshaw et al. 1986
11	Mink	(G)	1x		50	100 (incoordination)	300 (unconsciousness)	Hornshaw et al. 1986
Developmental								
12	Rat	(GO)	Gd6-15		175		450 (slight fetotoxicity)	BRRC 1988a
13	Rabbit	(GO)	Gd6-18		50		100 (slight fetotoxicity)	BRRC 1988b
Reproductive								
14	Rat	(GO)	Gd6-15		450			BRRC 1988a
15	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
INTERMEDIATE EXPOSURE								
Death								
16	Rat	(GO)	13 wk 7d/wk 1x/d		175		600 (death)	MBA 1988a
17	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d				450 (death)	BRRC 1989a
18	Ferret	(F)	28 d		400			Hornshaw et al. 1986
19	Mink	(F)	28 d		320			Hornshaw et al. 1986

TABLE 2-1a (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic								
20	Rat	(GO)	13 wk 7d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other	600 600 600 600 600 600 600 600 175	600 (decreased body weight gain)		MBA 1988a
21	rat	(GO)	16-20 wk 5-7 wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989a
22	Ferret	(F)	28 d	Resp Cardio Hemato Hepatic Renal Other	400 400 400 400 400 400			Hornshaw et al. 1986
23	Mink	(F)	28 d	Resp Cardio Hemato Hepatic Renal Other	320 320 320 320 320	320 (decreased body weight gain)		Hornshaw et al. 1986
24	Mink	(F)	6 mo	Other	25	105 (decreased body weight gain)		Hornshaw et al. 1986
Neurological								
25	Rat	(GO)	13 wk 7d/wk 1x/d			175 (tremors)	600 (coma, convulsions)	MBA 1988a

TABLE 2-1a (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
26	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986
27	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (ataxia, hypoactivity)		BRRC 1989a
Developmental								
28	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175	450 (decreased body weight of offspring		BRRC 1989a
29	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989a
Reproductive								
30	Mink	(F)	6 mo		105			Hornshaw et al. 1986

[a]The number corresponds to entries in Figure 2-1a.
[b]Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = time

TABLE 2-1b. Levels of Significant Exposure to p-Cresol - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	1x				1,800 (LD_{50})	Deichmann and Witherup 1944
Systemic								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other		50 (decreased body weight gain)		MBA 1988b
3	Rat	(GO)	2 wk 7d/wk 1x/d	Other		600 (decreased body weight gain, food intake)		TRL 1986
4	Rat	(GO)	Gd6-15	Resp	175	450 (audible respiration)		BRRC 1988a
				Hepatic	450			
				Other		450 (decreased body weight gain, food intake)		
5	Rabbit	(GO)	Gd6-18	Resp	5		50 (difficulty breathing)	BRRC 1988b
				Hepatic	100			
				Derm/oc	5	50 (ocular discharge)		
				Other	100			
Neurological								
6	Rat	(GO)	2 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988b
7	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
8	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
9	Rabbit	(GO)	Gd6-18		5[b]	50 (hypoactivity)		BRRC 1988b

TABLE 2-1b (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Developmental								
10	Rat	(GO)	Gd6-15		175		450 (slight fetotoxicity)	BRRC 1988a
11	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
Reproductive								
12	Rat	(GO)	Gd6-15		450			BRRC 1988a
13	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
INTERMEDIATE EXPOSURE								
Death								
14	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175		450 (death)	BRRC 1989b
Systemic								
15	Rat	(GO)	13 wk 7d/wk 1x/d	Resp	175	600 (epithelial metaplasia in trachea)		MBA 1988b
				Cardio	600			
				Gastro	600			
				Hemato	50	175 (decreased red blood cell count, hemoglobin)		
				Musc/skel	600			
				Hepatic	175	600 (increased SGOT, SGPT; inflammation)		
				Renal		50 (nephropathy)		
				Derm/oc	600			
				Other	175	600 (decreased body weight gain)		
16	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989b

TABLE 2-1b (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Neurological								
17	Rat	(GO)	13 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988b
18	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
19	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (perioral wetness)		BRRC 1989b
Developmental								
20	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175	450 (decreased body weight of offspring)		BRRC 1989b
Reproductive								
21	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989b

[a]The number corresponds to entries in Figure 2-1b.
[b]Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; wk = week; x = time

TABLE 2-1c. Levels of Significant Exposure to m-Cresol - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	1x				2,020 (LD_{50})	Deichmann and Witherup 1944
Systemic								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other		450 (decreased food intake)		TRL 1986
3	Rat	(GO)	Gd6-15	Resp	175	450 (audible respiration)		BRRC 1988a
				Hepatic	450			
				Other	175	450 (decreased body weight gain, food intake)		
4	Rabbit	(GO)	Gd6-18	Resp	5[b]	50 (audible respiration)		BRRC 1988b
				Hepatic	100			
				Derm/oc	5	50 (ocular discharge)		
				Other	100			
Neurological								
5	Rat	(GO)	2 wk 7d/wk 1x/d			450 (lethargy, tremors)		MBA 1988c
6	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986
7	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
Developmental								
8	Rat	(GO)	Gd6-15		450			BRRC 1988a
9	Rabbit	(GO)	Gd6-18		100			BRRC 1988b

TABLE 2-1c (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Reproductive								
10	Rat	(GO)	Gd6-15		450			BRRC 1988a
11	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
INTERMEDIATE EXPOSURE								
Death								
12	Rat	(GO)	16-20 wk 5-7d/wk 1x/d		175		450 (death)	BRRC 1988c
Systemic								
13	Rat	(GO)	13 wk 7d/wk 1x/d	Resp	450			MBA 1988c
				Cardio	450			
				Gastro	450			
				Hemato	450			
				Musc/skel	450			
				Hepatic	450			
				Renal	450			
				Derm/oc	450			
				Other		150 (decreased body weight gain)		
14	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989c
Neurological								
15	Rat	(GO)	13 wk 7d/wk 1x/d			450 (lethargy, tremors)		MBA 1988c
16	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986

TABLE 2-1c (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
17	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (perioral wetness)		BRRC 1989c
Developmental								
18	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175		450 (reduced pup survival)	BRRC 1989c
Reproductive								
19	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989c

[a]The number corresponds to entries in Figure 2-1c.
[b]Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = time

FIGURE 2-1a. Levels of Significant Exposure to o-Cresol - Oral

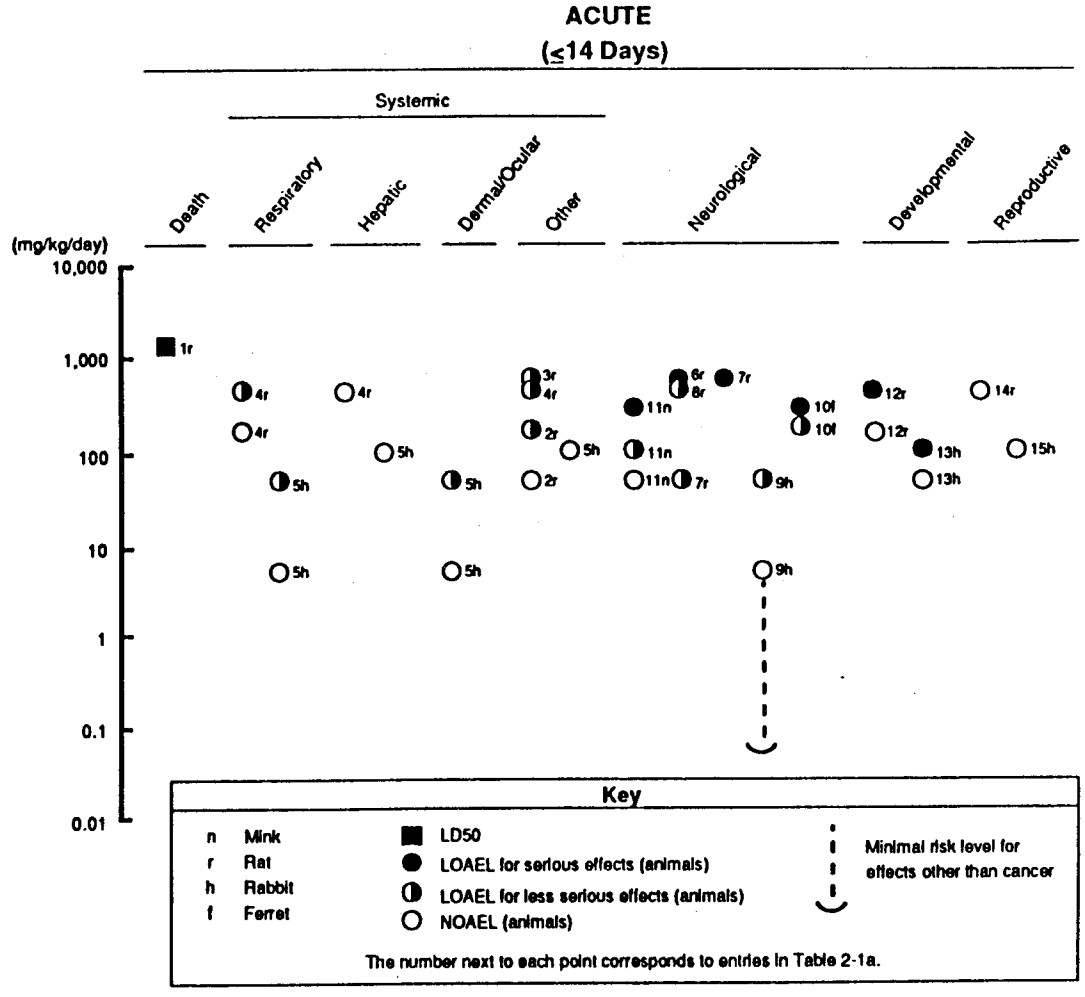


FIGURE 2-1a (Continued)

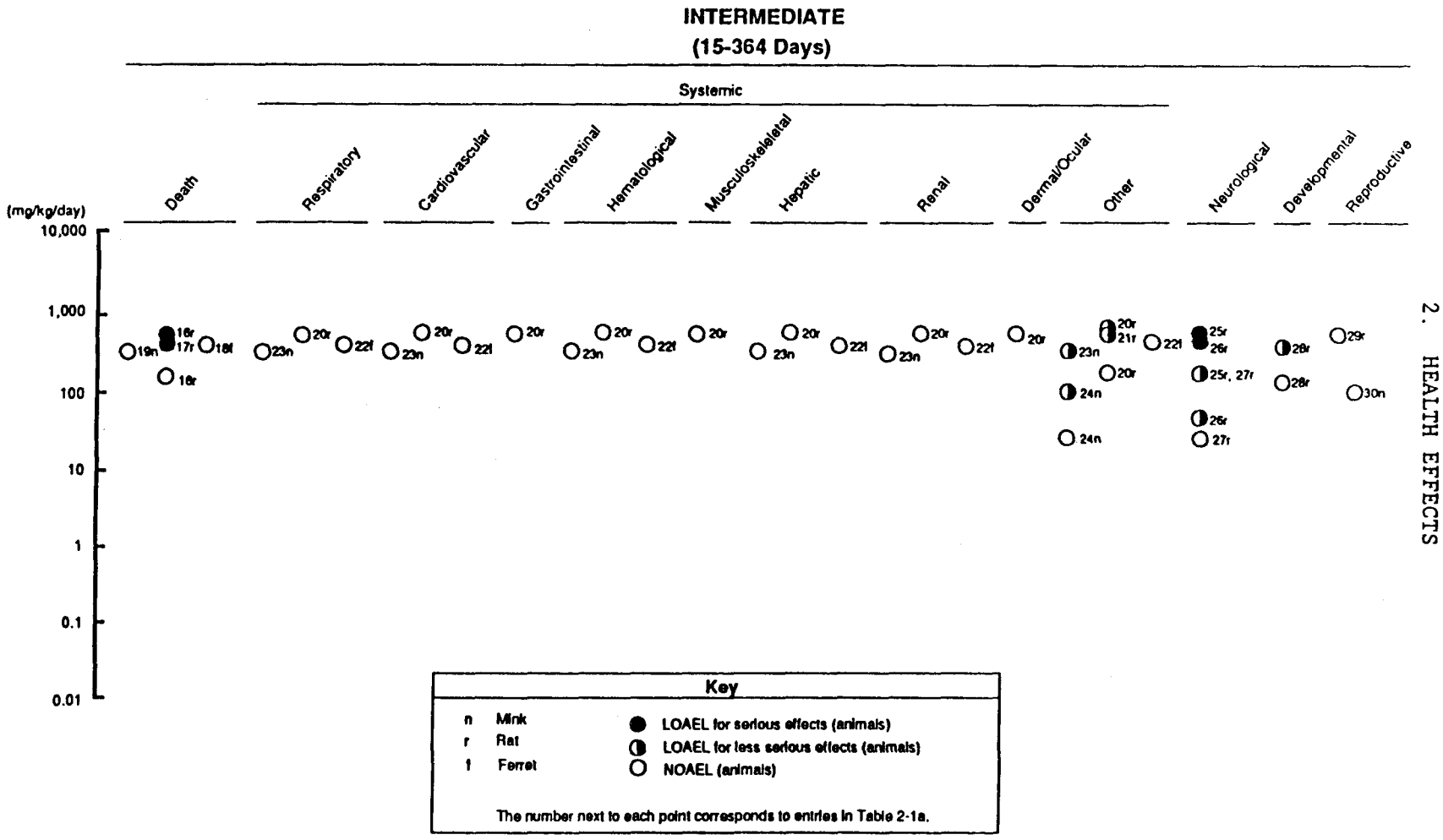


FIGURE 2-1b. Levels of Significant Exposure to p-Cresol - Oral

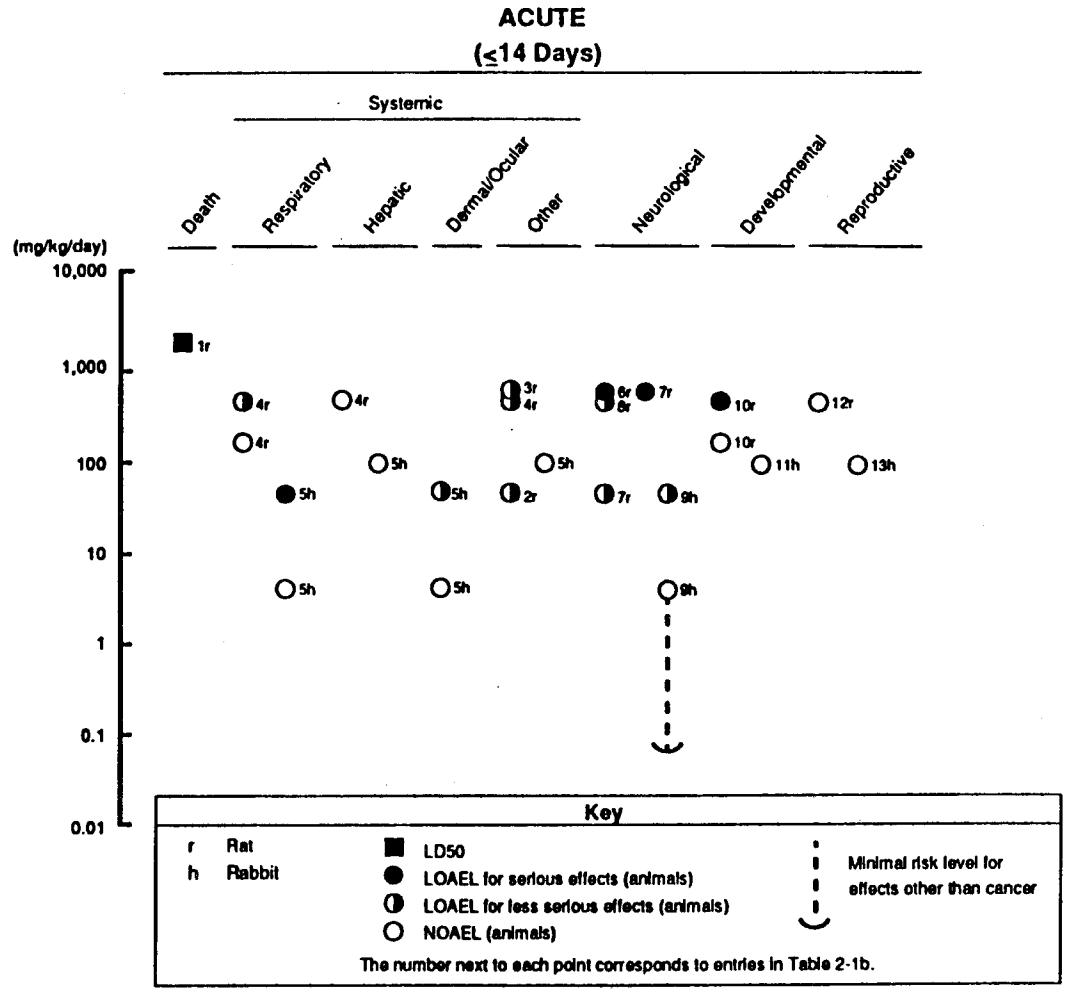


FIGURE 2-1b (Continued)

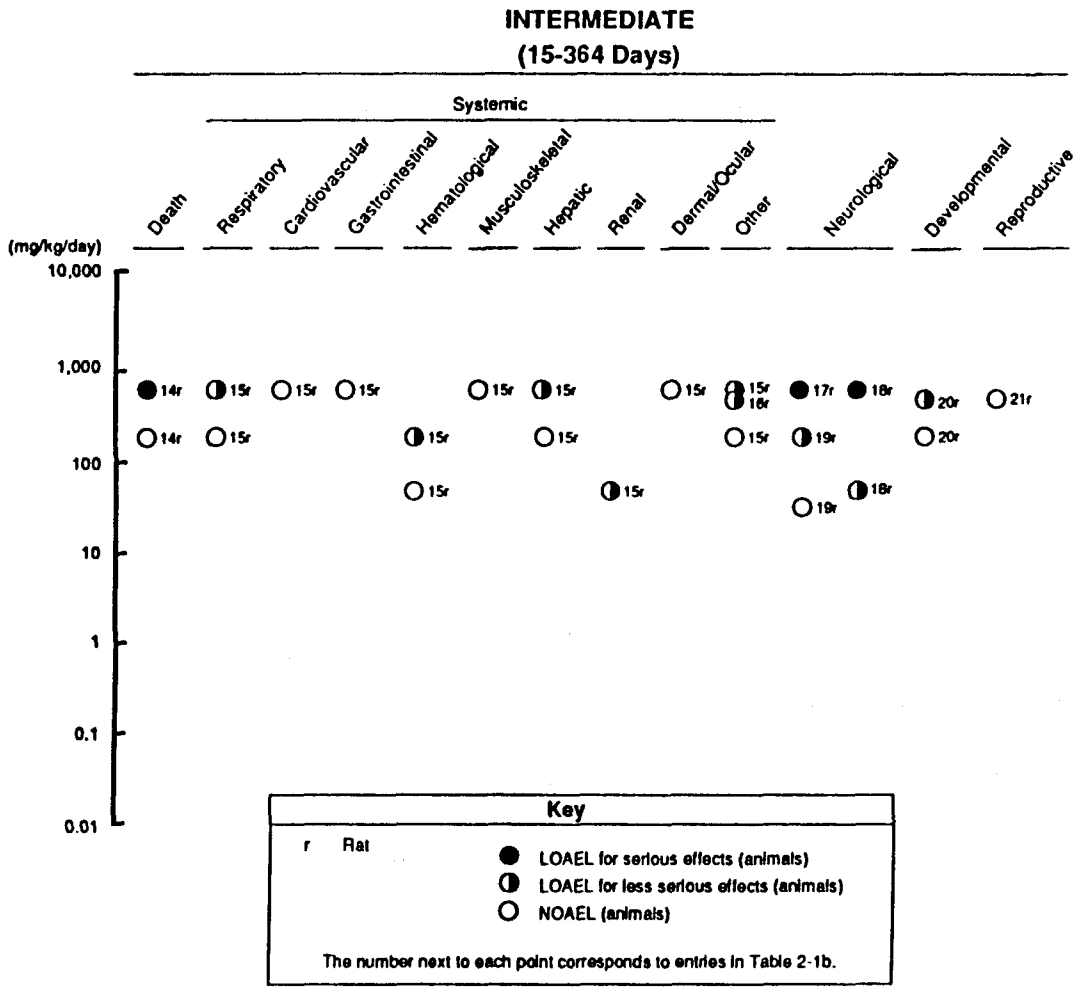


FIGURE 2-1c. Levels of Significant Exposure to m-Cresol - Oral

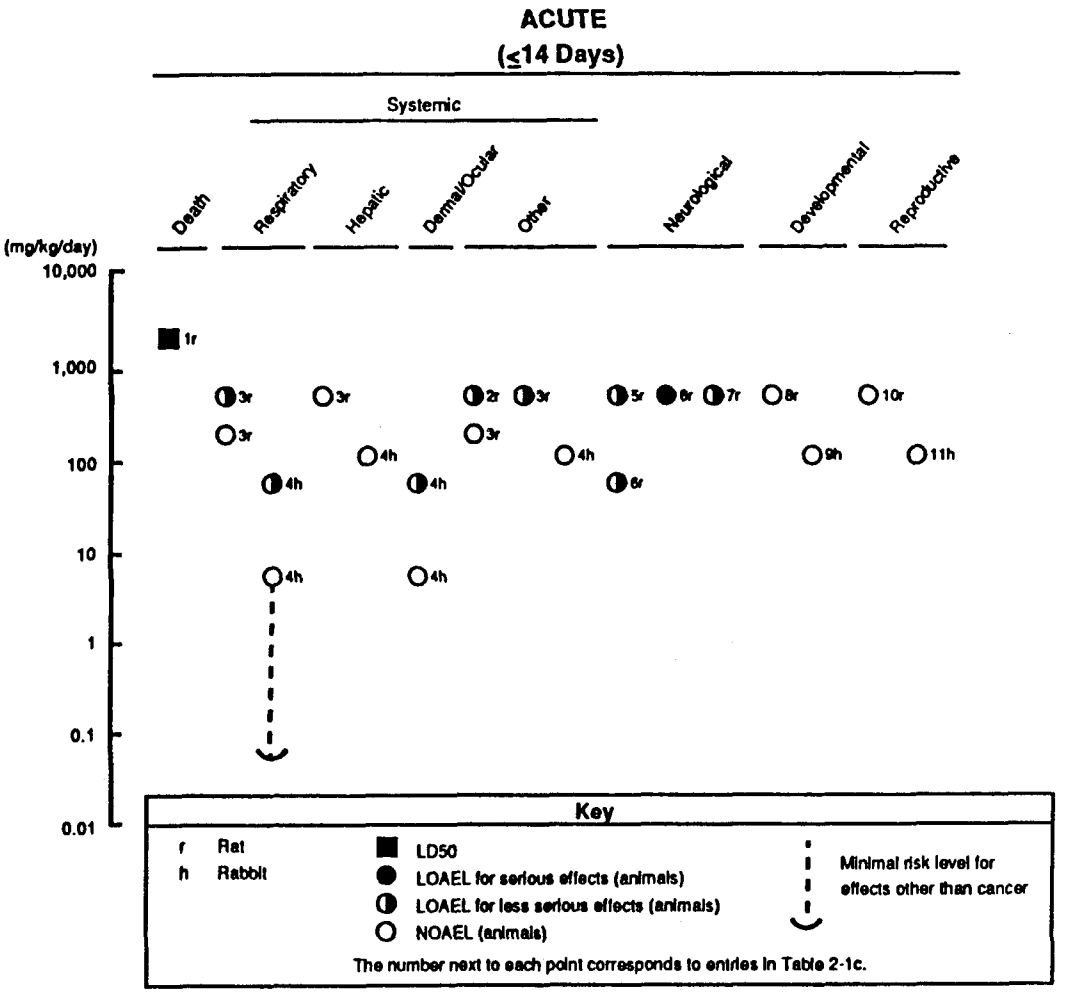
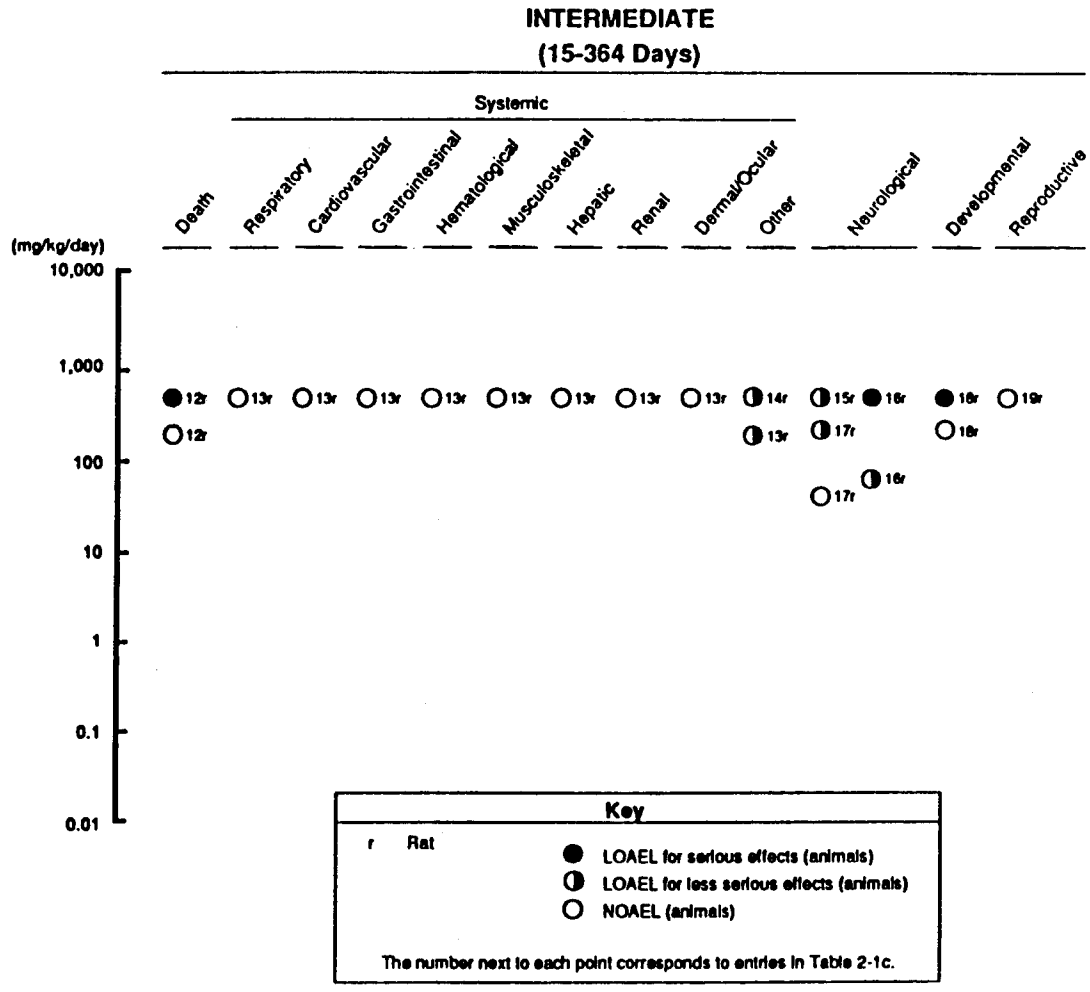


FIGURE 2-1c (Continued)



have been reported in animals exposed to cresols (Hornshaw et al. 1986; MBA 1988c), but the significance of these changes is doubtful without accompanying histological effects. Thus, the heart has not been shown to be a target organ for cresols.

Gastrointestinal Effects. Mouth and throat burns, abdominal pain, and vomiting were common symptoms of cresol poisoning among 52 patients who drank between 4 and 120 mL of a disinfectant containing 25%-50% mixed cresols (Isaacs 1922). These effects were also seen in a man who swallowed approximately 250 mL of a concentrated cresol mixture in a suicide attempt (Jouglard et al.1971). Hemorrhagic degeneration of the pancreas was the cause of death in a woman who swallowed a disinfectant suspected of containing cresols. It was not clear, however, if this effect was actually produced by the disinfectant or was due to a pre-existing condition (little disinfectant was taken) (Dellal 1931).

Rats exposed to cresols for 13 weeks by gavage in corn oil did not have gastrointestinal lesions (MBA 1988a, 1988b, 1988c). However, p-cresol given in the feed produced an increased incidence of mild and moderate hyperplasia of the forestomach of hamsters exposed for 20 weeks (Hirose et al. 1986). This result suggests that p-cresol may have the potential to act as a promoter in forestomach carcinogenesis. Rats exposed to a similar concentration in the feed for a shorter time period did not have this effect, although this species is, in general, less sensitive to inducers of forestomach lesions (Altmann et al. 1986). Insufficient data were provided to derive doses given in the two feeding studies, so these studies were not used to derive NOAEL or LOAEL values.

Hematological Effects. Hematological effects were described in four people who ingested cresol-containing products. One woman swallowed 100 mL of a disinfectant containing 50% mixed cresols, receiving a dose of approximately 1 g/kg (Chan et al. 1971). Methemoglobin was seen in the blood after 1.5 hours, but was no longer detected after 6 hours. Some Heinz bodies were observed after 6 hours, but these disappeared after 2 days. A second woman, who drank 250 mL of disinfectant (roughly 2 g/kg), experienced more serious effects. Methemoglobinemia and markedly reduced glutathione levels were seen after 7 hours. After 3 days, the patient developed severe hemoglobinemia and hemoglobinuria, indicating that massive intravascular hemolysis had occurred; extensive Heinz body formation had also taken place. The patient died the next day, apparently from thrombus formation and kidney failure secondary to acute intravascular hemolysis (Chan et al. 1971). Heinz body formation, hemoglobinemia, hemoglobinuria, and hemolytic anemia were also seen in a man who drank 100 mL of penetrating oil containing 12% mixed cresols, receiving a dose of about 170 mg/kg (Cote et al. 1984). In addition, a man who swallowed approximately 250 mL of a concentrated cresol mixture developed severe hemolytic anemia during the second week following ingestion (Jouglard et al. 1971). Isaacs (1922) did not find abnormalities in the blood of any of 52

patients who had ingested cresols, but the specific analyses performed were not reported. The hematological effects of cresols appear to be due to both an oxidant effect on the cell contents and a direct effect on the red cell membrane (Chan et al., 1971).

Severe hematological effects, such as those reported in humans, were not observed in animals exposed to cresols possibly because acute high-dose studies in animals did not investigate hematological effects. Mild decreases in red blood cells, blood hemoglobin concentrations, and hematocrit were reported in rats exposed to 175 mg/kg of p-cresol for 13 weeks (MBA 1988b), but the effects were not produced by the other isomers (MBA 1988a, 1988c). Mild and contradictory changes in red blood cell count seen in mink were of questionable significance (Hornshaw et al. 1986). Based on the available information, oral exposure to cresols at 175 mg/kg/day or above may be associated with changes in red blood cell and hematocrit in animals.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to cresols.

Cresols had no effect on the incidence of gross or microscopic lesions in the muscle or bone of rats given doses up to 600 mg/kg/day for 13 weeks (MBA 1988a, 1988b, 1988c).

Hepatic Effects. Moderate fatty degeneration was found in the liver of a woman who died after drinking 250 mL of a disinfectant, which contained 50% mixed cresols (Chan et al. 1971). The liver appeared normal in another woman who died after ingesting a disinfectant suspected of containing cresols (Dellal 1931).

Following oral exposure of animals to cresols, increased relative liver weight and increased serum transaminase levels were reported. Relative liver weights in rats increased following exposure to high levels (450 mg/kg/day) of cresols during pregnancy (BRRC 1988a). Longer-term exposure to levels as low as 5 mg/kg/day had the same effect in mink and ferrets (Hornshaw et al. 1986). However, in these studies, changes in liver weight were not accompanied by histological changes and may not have indicated adverse effects. Increased levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were seen in female rats given 600 mg/kg/day of p-cresol for 13 weeks and appeared to be correlated with the presence of hepatic inflammation (MBA 1988b).

Renal Effects. Massive eosinophilic necrosis was found in the proximal tubule of a woman who died after drinking 500-750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was considered by the investigators to have occurred before death, and may have been due to the toxic action of cresol. Renal effects in a woman who drank 250 mL of a disinfectant (50% mixed cresols), and later died, consisted of fibrin clumps

in the glomeruli and a moderate level of tubular degeneration, which could have been due to intravascular thrombosis (Chan et al. 1971). Mild congestion of the kidney was reported in a second woman who died following consumption of a disinfectant suspected of containing cresols (Dellal 1931). Among 52 patients with diagnosed cresol poisoning, there were signs of renal toxicity, including darkly colored urine, renal irritation, and in a few cases, reduced phenolsulphonephthalein output (Isaacs 1922).

Effects seen in animals orally exposed to cresols included mild increases in kidney weight (Hornshaw et al. 1986; MBA 1988b) and a slight increase, which did not appear to be dose related, in the incidence of histological changes characteristic of chronic nephropathy in male rats exposed to p-cresol for 13 weeks (MBA 1988b). No changes were seen in similar studies of o- and m-cresol (MBA 1988a, 1988c). The evidence is not conclusive as to whether the kidney is a target organ of cresol toxicity in animals.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following oral exposure to cresols.

Pregnant rabbits repeatedly given 50 mg/kg/day or more of the cresol isomers during gestation were found to have significant amounts of ocular discharge, some of which may have been due to hemorrhaging (BRRC 1988b), but no gross or microscopic lesions of the eye or skin were found in rats given cresols orally for 13 weeks (MBA 1988a, 1988b, 1988c).

Other Systemic Effects. No studies were located regarding other systemic effects in humans following oral exposure to cresols.

In animals, a common response to oral cresols exposure was decreased growth, often associated with decreased food consumption (BRRC 1988a, 1989a, 1989b, 1989c; Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c; TRL 1986). The lowest dose to produce this effect in a systemic toxicity study was 50 mg/kg/day of p-cresol in rats (MBA 1988b). An even lower dose, 30 mg/kg/day of m-cresol, produced low body weight in F_1 adult rats in a two-generation reproduction study (BRRC 1989c). None of these studies involved pair-feeding protocols, so the significance of any reported weight gain reductions is uncertain, even though food consumption was usually monitored as well.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans following oral exposure to cresols.

No immunotoxicity tests were included in acute animal studies, and the only immunological end points examined in longer-term animal studies were spleen weight and histopathology. Spleen weight was unaffected by 28-day

exposure to o-cresol in the feed at doses up to 400-720 mg/kg/day in ferrets and 320-480 mg/kg/day in mink (Hornshaw et al. 1986). Similarly, no effect was seen on spleen weight in a reproduction study in which mink were exposed to 105-190 mg/kg/day of o-cresol in the feed for 6 months (Hornshaw et al. 1986). Absolute spleen weight was decreased (approximately 18%) in male rats given 600 mg/kg/day of p-cresol for 13 weeks, but relative spleen weight was unaffected and no lesions were found (MBA 1988b); no changes were found in rats given o- or m-cresol (MBA 1988a, 1988c). NOAEL values were not derived from these studies because these end points are not sufficiently sensitive to assess subtle immunological effects.

2.2.2.4 Neurological Effects

Neurological effects have frequently been noted following oral exposure to cresols. A woman who drank approximately 100 mL of a disinfectant, which consisted of roughly 50% mixed cresols, was semiconscious after 2 hours. A second woman, who swallowed about 250 mL of the same disinfectant, was in a deep coma after 2 hours. She regained consciousness 10 hours later (Chan et al. 1971). A woman who swallowed 500-750 mL of a concentrated cresol mixture fell into a deep coma within 1 hour (Labram and Gervais 1968). Coma was a common feature of cresol poisoning among 52 patients studied by Isaacs (1922). The author noted that unconsciousness could occur very soon after exposure and could last 14 hours or more.

A series of neurological effects, including hypoactivity and lethargy, excess salivation, dyspnea, incoordination, muscle twitches and tremors, convulsions, and coma, has been reported in animals acutely exposed to cresols (BRRC 1988a, 1988b; Deichmann and Witherup 1944; Hornshaw et al. 1986; TRL 1986). The lowest dose at which neurological effects were reported was 50 mg/kg/day, which produced hypoactivity and audible respiration in pregnant female rabbits repeatedly dosed with o- or p-cresol during gestation (BRRC 1988b). Based on the NOAEL values of 5 mg/kg/day for o- and p-cresol in this study, acute oral MRLs of 0.05 mg/kg/day were calculated, as described in footnote b in Tables 2-la and 2-lb. In rats, effects such as hypoactivity, rapid labored respiration, and hyperreactivity were seen at 50 mg/kg/day for all three isomers (TRL 1986). More serious effects, such as convulsions, were seen at 450 mg/kg/day or higher (TRL 1986).

A detailed oral neurotoxicity study of intermediate duration was performed on rats using all three cresol isomers (TRL 1986). A host of clinical observations indicative of neurotoxicity (including hypoactivity, rapid labored respiration, excessive salivation, and tremors) was reported at doses of 50 mg/kg/day or higher for all three isomers. However, the results of few neurobehavioral tests were significantly altered by treatment, and no brain weight changes or histopathologic lesions in the brain or other nervous tissues were found for any isomer. Convulsions were reported at 450 mg/kg/day or higher (TRL 1986). Other studies of prolonged oral exposure to cresols had similar findings (BRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986; MBA l988a,

1988b, 1988c). The only intermediate-duration studies to determine NOAEL values for neurological effects were the two-generation reproduction studies in rats (BRRC 1989a, 1989b, 1989c). Neurological NOAEL values of 30 mg/kg/day were reported for all three cresol isomers in these studies.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Tables 2-la, 2-lb, and 2-1c and plotted in Figures 2-la, 2-lb, and 2-1c.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to cresols.

Developmental effects have been reported in animals given cresols, but only at maternally toxic doses. Maternal effects in rats dosed throughout gestation (audible respiration, reduced body weight gain, reduced food consumption, ataxia, tremors, and,hypoactivity) occurred at 450 mg/kg/day. At this dose, both o- and p-cresol produced slight fetotoxicity (increased incidences of dilated lateral ventricles in the brain and minor skeletal variations, respectively), but had no effect on malformation incidence or gestation parameters (e.g., the number of implantations per litter or fetal body weight per litter). No effects of any kind were seen at lower doses. m-Cresol had no effect on gestation parameters, fetotoxicity, or the incidence of malformations, even at maternally toxic doses (BRRC 1988a). In rabbits dosed throughout gestation, maternal effects, such as audible respiration, ocular discharge, and hypoactivity, were seen following exposure to o- or p-cresol at 50 mg/kg/day. At 100 mg/kg/day, o-cresol produced slight fetotoxicity (increased incidences of subepidermal hematoma on the head and poorly ossified sternebrae), but no other effects at any dose. Neither p- nor m-cresol produced any developmental effects in this study (BRRC 1988b).

Fetotoxicity was also observed at parenterally-toxic doses in two-generation reproduction studies. Rats treated with 450 mg/kg/day of o- and p-cresol produced F_1 offspring that had reduced body weight 4-6 weeks after birth. This dose also produced overt toxicity in the parents (BRRC 1989a, 1989b). In contrast to the results of the developmental toxicity studies discussed above, m-cresol was the most potent developmental toxicant among the cresols in the two-generation studies. This isomer produced effects on body weight of offspring at the low dose of 30 mg/kg/day and reduced pup survival during lactation at the high dose of 450 mg/kg/day (BRRC 1989c). Parental toxicity was also reported at the low dose of 30 mg/kg/day, but the possibility remains that developmental effects could occur at doses lower than those producing parental toxicity; therefore, this study is inconclusive regarding the developmental toxicity of this isomer.

NOAEL and LOAEL values derived from these studies are recorded in Tables 2-la, 2-lb, and 2-1c and plotted in Figures 2-la, 2-lb, and 2-1c.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to cresols.

No reproductive effects were seen in animals exposed to cresols by ingestion. Developmental toxicity studies in which pregnant rats (BRRC 1988a) and rabbits (BRRC 1988b) were exposed to cresols during gestation reported no effects on the reproductive parameters investigated (e.g., number of ovarian corpora lutea, number of implantation sites, number of viable fetuses), even at maternally toxic doses. Two-generation reproduction studies in rats and mink also failed to detect adverse effects on reproductive function or lesions in reproductive tissues (BRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986). These studies also included doses producing maternal toxicity. No histopathological lesions and only mild organ weight changes of doubtful significance were reported in the reproductive organs of animals exposed to cresols for prolonged periods in other studies (Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c). NOAEL values derived from these studies are recorded in Tables 2-la, 2-lb, and 2-1c and plotted in Figures 2-la, 2-lb, and 2-1c.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to cresols.

Dominant lethal assays in mice were performed using o- and p-cresols. Male mice were given a single dose of o-cresol (0, 75, 250, or 750 mg/kg) or p-cresol (0, 100, 275, or 550 mg/kg) by gavage in corn oil and mated to untreated females in order to assess dominant lethal effects. The matings were continued for 6 weeks so that all stages of male germ cell development were tested. Exposure to neither cresol isomer had any effect on the occurrence of dominant lethal mutations in mice (Hazleton Labs 1989a, 1989b). m-Cresol was tested for ability to induce chromosomal aberrations in mouse bone marrow in vivo. Male and female mice were given a single dose of 0, 96, 320, or 960 mg/kg by gavage in corn oil and sacrificed after 6, 24, and 48 hours for extraction and examination of bone marrow. No effect on chromosomal aberrations was found (Hazleton Labs, 1989c).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to cresols.

Lifetime cancer bioassays using orally exposed animals were not located. In a shorter-term study, exposure to p-cresol in the feed for 20 weeks produced an increased incidence of forestomach hyperplasia in hamsters,

suggesting that this cresol isomer may have the potential to act as a promoter of forestomach carcinogenesis in this species (Hirose et al. 1986). However, promotion potential was not tested directly. p-Cresol did not produce forestomach hyperplasia in rats (Altmann et al. 1986), but rats are generally less sensitive than hamsters to inducers of forestomach lesions.

2.2.3 Dermal Exposure

2.2.3.1 Death

There are two case reports of people who died following dermal exposure to cresols. In one case, a l-year-old baby had 20 mL of a cresol derivative (90% mixed cresols in water) spilled on his head, covering about 7% of his body surface. The baby died in coma within 4 hours (Green 1975). Assuming the baby weighed approximately 10 kg, the lethal dose in this case can be estimated to have been roughly 2 g/kg. In the other case, a man fell into a vat of a cresylic acid derivative (cresol content unknown) and suffered burns on 15% of the body surface. Anuria was evident after 36 hours and blood urea content rose steadily during the following days. The patient fell into a coma on the 9th day, and death occurred on the 10th day (Cason 1959). Dermal absorption of cresol also appears to have been responsible for the death of a man who worked with an antiseptic solution containing concentrated mixed cresols for 2 days prior to becoming ill (Larcan et al. 1974).

In rabbits, dermal LD_{50} values for cresols were 890, 300, 2,830, and 2,000 mg/kg for o-, p-, m-, and mixed cresols, respectively (Vernot et al. 1977). These values are recorded in Table 2-2. Based on these LD_{50} values, p-cresol appears to be more toxic dermally than o-cresol, with m-cresol being the least toxic of the three isomers.

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular or musculoskeletal effects in humans or animals following dermal exposure to cresols.

Respiratory Effects. Hemorrhagic pulmonary edema was found at necropsy in a l-year-old baby who died after having 20 mL of a cresol-containing product spilled on his head (Green 1975).

No studies were located regarding respiratory effects in animals following dermal exposure to cresols.

Gastrointestinal Effects. No lesions were found in the gastrointestinal tract of a l-year-old baby who died after dermal exposure to a cresol-containing product (Green 1975).

TABLE 2-2. Levels of Significant Exposure to Cresols - Dermal

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Isomer
ACUTE EXPOSURE							
Death							
Rabbit	1 d 24hr/d				890 (LD_{50})	Vernot et al. 1977	o-
Rabbit	1 d 24hr/d				300 (LD_{50})	Vernot et al. 1977	p-
Rabbit	1 d 24hr/d				2,830 (LD_{50})	Vernot et al. 1977	m-
Rabbit	1 d 24hr/d				2,000 (LD_{50})	Vernot et al. 1977	mix
Systemic							
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	o-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	p-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	m-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	mix

d = day; Derm/oc = dermal/ocular; hr = hour; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

No studies were located regarding gastrointestinal effects in animals following dermal exposure to cresols.

Hematological Effects. Hematological effects in a man, apparently exposed to cresol dermally while working with an antiseptic solution containing concentrated mixed cresols, included methemoglobinemia with massive hemolysis and the presence of numerous large Heinz bodies in the blood (Larcan et al. 1974). Similar effects have been reported following oral exposure to cresols (see Section 2.2.2.2).

No studies were located regarding hematological effects in animals following dermal exposure to cresols.

Hepatic Effects. Necropsy revealed extensive centrilobular to mid-zonal liver necrosis in a l-year-old baby who had 20 mL of a cresol derivative spilled on his head (Green 1975).

No studies were located regarding hepatic effects in animals following dermal exposure to cresols.

Renal Effects. A l-year-old baby who died after a cresol derivative was spilled on his head had congested and swollen kidneys that were damaged by tubular necrosis (Green 1975). A man who fell into a vat containing a cresylic acid derivative developed anuria after 36 hours and experienced a steady increase in blood urea levels for 10 days until he died (Cason 1959). Anuria was also seen in a man who apparently absorbed cresol through the skin while working with an antiseptic solution containing concentrated mixed cresols (Larcan et al. 1974).

No studies were located regarding renal effects in animals following dermal exposure to cresols.

Dermal/Ocular Effects. Corrosive damage to the skin has been reported in humans dermally exposed to cresols (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985). In one patient, disfiguring scars remained visible 1 year after exposure (Herwick and Treweek 1933). However, no reaction to cresol was noted when it was applied to the skin as a 1% solution in alcohol (Reimann 1933).

Cresols are also strong skin irritants in animals. All three cresol isomers, either alone or in combination, are severely irritating to rabbit skin, producing visible and irreversible tissue destruction (Vernot et al. 1977). Some cresylic acids produced induration and discoloration of the skin in rats (Campbell 1941). All reliable LOAEL values for acute dermal effects in rabbits are recorded in Table 2-2.

In a study of intermediate duration, dermal application of 0.5% p-cresol for 6 weeks produced permanent depigmentation of the skin and hair of mice (Shelley 1974). A caustic effect on the skin was noted in one strain of mouse, but not another. Neither o- nor m-cresol produced any color change in the mice. The author suggests that only p-cresol is active because it mimics the structure of tyrosine, the amino acid present in melanin, so that tyrosinase acts on it, liberating free radicals that damage melanocytes. NOAEL and L0AEL values were not derived from this study because the applied dose was not reported.

Other Systemic Effects. No studies were located regarding other systemic effects in humans or animals following dermal exposure to cresols.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to cresols.

2.2.3.4 Neurological Effects

Neurological effects were seen in two people who were accidentally exposed to mixed cresols on the skin and later died. A l-year-old baby who had 20 mL of a cresol derivative spilled on his head was unconscious within 5 minutes; autopsy revealed swelling and congestion of the brain (Green 1975). A man who fell into a vat containing a cresylic acid derivative and received burns on 15% of his body fell into a coma 9 days later (Cason 1959). A man who survived 5-6 hour immersion of his hands in a concentrated cresylic acid solution experienced persistent eye watering, followed by pain on the side of his face and, ultimately, marked facial paralysis (Klinger and Norton 1945).

Only one study reported neurological effects in animals following dermal exposure to cresols. Rapid, shallow breathing and convulsions were observed in rats 5-30 minutes after covered dermal application of 1.0-3.5 mL/kg of certain cresylic acid formulations (Campbell 1941). Other formulations had no effect. These convulsions stopped after a few hours in the rats that survived.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cresols:

2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans following dermal exposure to cresols.

Cresols have not been evaluated for ability to induce cancer when applied to the skin of animals. However, a study of skin tumor promotion by cresols was located (Boutwell and Bosch 1959). Mice were given a single dermal application of 9,10-dimethyl-1,2-benzanthracene (DMBA), a cancer initiator, followed by application of 20% solutions of o-, p-, or m-cresol in benzene twice a week for 12 weeks. This level of cresols exposure proved to be acutely toxic, producing relatively high nontumor-related mortality. Consequently, all tumor results were based on number of survivors (14-20 per group) . Promotion with cresols led to increases in the average number of skin papillomas per mouse and the percentage of exposed mice with at least one papilloma. o-Cresol was the most potent isomer, and p-cresol the least. Carcinomas were not observed following cresols exposure, although the observed papillomas have the potential to develop into carcinomas. A problem with the study was use of benzene, a known carcinogen, as the solvent for the cresols. However, benzene controls in the cresols experiment did not develop papillomas, and neither did benzene controls in four parallel series of experiments (a few papillomas were observed in a fifth benzene control group). Therefore, the results of this study showing that all three cresol isomers are capable of promoting skin tumors initiated by DMBA appear to be valid. The EPA has assigned all three cresol isomers to cancer group C as possible human carcinogens based on the results of this study (IRIS 1991).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans following inhalation exposure to cresols.

The absorption of cresols following inhalation exposure in animals has not been quantified but can be assumed to occur, since mortality and other effects have been reported in animals following exposure (Campbeil 1941; Kurlyandsky et al. 1975; Uzhdavini et al. 1972).

2.3.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans following oral exposure to cresols.

Rabbits were orally exposed to all three cresol isomers by Bray et al. (1950). From 65% to 84% of the administered dose was recovered in the urine within 24 hours, indicating that at least that amount had been absorbed.

2.3.1.3 Dermal Exposure

The occurrence of coma, death, and systemic effects in two humans dermally exposed to cresols (Cason 1959; Green 1975) indicates that these compounds can be absorbed through the skin. No studies were located that sought to quantify the rate or extent of absorption in intact humans. An in vitro study of the permeability of human skin to cresols found that these substances had permeability coefficients greater than that for phenol, which is known to be readily absorbed across the skin in humans (Roberts et al. 1977).

No studies were located regarding the rate and extent of absorption in animals following dermal exposure to cresols.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the extent of distribution in humans or animals following inhalation exposure to cresols.

2.3.2.2 Oral Exposure

No studies were located regarding the extent of distribution in humans or animals following oral exposure to cresols.

2.3.2.3 Dermal Exposure

Cresols were identified in the blood (12 mg/l00 mL), liver, and brain of a l-year-old baby who died 4 hours after 20 mL of a cresol derivative was spilled on his head (Green 1975).

No studies were located regarding the extent of distribution in animals following dermal exposure to cresols.

2.3.3 Metabolism

No studies were located regarding metabolism in humans following exposure to cresols.

A few studies reported on the metabolism of cresols in animals. Cresols in the urine are found primarily as sulfate and glucuronide conjugates. In the urine of rabbits, 60%-72% of the orally administered dose was recovered as ether glucuronide, and 10%-15% was recovered as ethereal sulfate (Bray et al.

1950). A similar result was obtained in an earlier study in rabbits in which 14.5%-23.5% of the orally administered dose was found conjugated with sulfate in the urine (Williams 1938). For simple phenols such as cresols, the proportions of the conjugates are known to vary with dose and to differ from one species to the next. In the study by Bray et al. (1950), hydroxylation of a small percentage (3%) of the administered dose to 2,5-dihydroxytoluene (conjugated) occurred for both o- and m-cresol. No hydroxylation occurred for p-cresol, but p-hydroxybenzoic acid (both free and conjugated) was detected in the urine. Only 1%-2% of the administered dose was found as unconjugated free cresol in the urine.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals following inhalation exposure to cresols.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to cresols.

Following oral exposure to cresols in rabbits, 65%-84% of the dose was excreted in the urine within 24 hours, mostly as ethereal glucuronides and sulfates (Bray et al. 1950).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to cresols.

2.4 RELEVANCE TO PUBLIC HEALTH

Effects associated with exposure to cresols in humans include irritation and burning of skin, eyes, mouth, and throat, abdominal pain and vomiting, tachycardia and ventricular fibrillation, hemolytic anemia, liver and kidney damage, facial paralysis, coma, and death. Studies in animals have documented the irritative and neurological effects of cresols, and provided some evidence for target organ effects on the kidney, liver, and the blood. Other effects seen in animals, but not observed in humans, include slightly reduced body weight gain, mild developmental effects, and tumor promotion.

Inhalation MRLs were not derived for cresols due to the lack of acceptable data. Acute oral MRLs for o-, p-, and m-cresols were based on the occurrence of neurological effects (and secondary respiratory stress) in exposed animals. For all three cresol isomers, the acute MRL was calculated to be 0.05 mg/kg/day by applying an uncertainty factor of 100 (10 for

extrapolation from animals to humans and 10 for human variability) to the NOAEL for neurological/respiratory effects of 5 mg/kg/day obtained in pregnant rabbits dosed during gestation (BRRC 1988b). The most prominent neurological/respiratory effects observed at the LOAEL of 50 mg/kg/day were hypoactivity and audible respiration. Similar effects were reported in rats exposed to 50 mg/kg/day in a study specifically designed to investigate neurological effects (TRL 1986).

Intermediate oral MRLs for all three cresol isomers could have been calculated based on NOAEL values of 30 mg/kg/day for neurological effects in two-generation reproductive studies in rats (BRRC 1989a, 1989b, 1989c). However, these intermediate oral MRLs were not derived because they would have been less protective than the acute MRLs. This apparent anomaly reflects the fact that lower doses were employed in the developmental toxicity study used as the basis for the acute MRLs than in longer term studies. Dermal MRLs were not derived for cresols due to the lack of an appropriate methodology.

Death. Human deaths have occurred following ingestion or dermal exposure to highly concentrated solutions of cresols and as a result of intentional intravaginal or intrauterine exposure for the purpose of inducing abortion (Finzer 1961; Presley and Brown 1956; Vance 1945). Exposure levels associated with human deaths have not been reliably reported. However, based on crude estimates for cases of accidental or intentional ingestion of cresol-containing formulations, the lethal oral exposure level for humans appeared to be at or above 2 g/kg (Chan et al. 1971). The lethal dose was also approximately 2 g/kg following dermal exposure (Green 1975). Death following cresol exposure is apparently caused by intravascular hemolysis and thrombosis.

Studies in animals have shown that cresols can be lethal when exposure is through the inhalation, oral, or dermal routes. The lethal exposure levels varied from 1,350 to 2,020 mg/kg in orally exposed rats and 300 to 2,830 mg/kg in dermally exposed rabbits, depending on the isomer tested. By either route, m-cresol was the least toxic isomer. Lethal levels were not determined in inhalation studies, but one study (Campbell 1941) reported that brief repeated inhalation exposures produced lethality at concentrations that were not lethal when a single, longer exposure period was used. The estimated lethal dose in humans (2,000 mg/kg) is within the range of values reported in other species. Other observations regarding the lethality of cresols to animals might also apply to acutely-exposed humans.

Systemic Effects. Effects reported in humans include mucosal irritation following inhalation; mouth and throat burns, abdominal pain, vomiting, tachycardia and ventricular fibrillation, hemolytic anemia, and impaired kidney function following ingestion of highly concentrated solutions; and hemolytic anemia, anuria, elevated blood urea levels, and severe skin corrosion following spilling of highly concentrated solutions on the skin.

Autopsies of people who died following cresol exposure revealed gross lesions in the lungs, pancreas, liver, and kidneys, although these data cannot be considered reliable indicators of target organ effects. Data from animalstudies generally support the portal of entry effects reported in humans, such as mucosal irritation following inhalation, gastrointestinal irritation following oral administration, and severe skin damage following dermal application. Other effects, such as hemolytic anemia, have not been reported in animals; however, the doses given in the animal studies that examined toxic effects to the blood are probably well below those to which the humans were exposed. Other acute effects reliably reported to occur in animals include labored breathing, ocular discharge, and reduced body weight gain.

No longer-term exposure data are available for humans. In rats, intermediate-duration oral exposure to o- or m-cresol produced reductions in body weight gain and occasional organ weight changes. In addition to these effects, p-cresol produced some more notable changes, such as an increased incidence of epithelial metaplasia in the trachea, mild reductions in hemoglobin, hematocrit and red blood cell counts, increased serum transaminase levels (indicative of liver damage and associated with liver inflammation in this study), and mild nephropathy. It is not known if similar changes would occur in humans if they were exposed to cresols for extended periods.

Immunological Effects. Immunological effects of cresols in humans have not been reported. The immunotoxicity potential of cresol has not been evaluated in animals.

Neurological Effects. Coma has frequently been noted in case reports of humans exposed to highly concentrated cresols taken in the mouth or spilled on the skin. Facial paralysis was observed in one case of dermal exposure. Coma has also been observed in animals exposed to high doses. Other neurological effects observed in animals include lethargy, incoordination, muscle tremors, and convulsions. Cresols produce neurological effects following oral, dermal, and inhalation exposure, and although severity increases with dose, even low doses produce some of these effects. The acute oral MRL of 0.05 mg/kg/day was based on hypoactivity in pregnant female rabbits. CD_{50} values (dose that produced convulsions in l/2 of the animals tested) for the production of myoclonic convulsions in anesthetized mice given cresols by intraperitoneal injection were similar for all three isomers, increasing from 102 mg/kg for mcresol to 110 mg/kg for p-cresol to 117 mg/kg for o-cresol (Angel and Rogers 1972). No reliable studies have reported structural damage to the nervous system or other irreversible effects. The mechanism by which cresols affect the nervous system is unknown. Studies attempting to investigate cresol. neurotoxicity from a mechanistic point of view have reported enzymatic changes in the brains of rats after extended oral exposure to o-cresol (Savolainen 1979), and excitation of somatosensory evoked potential and electroencephalogram at levels producing muscle tremors and hyperactivity in rats that were acutely exposed to intravenous o-cresol (Mattsson et al. 1989).

Although only severe neurological effects have been reported in humans, the occurrence of less severe effects in animals suggests that these more subtle effects might occur in humans as well, but at doses far lower than those producing gross effects.

Developmental Effects. No developmental effects have been reported in humans exposed to cresols. Slightly elevated incidences of minor variations in rats and rabbits exposed to o- and p-cresols at maternally toxic doses indicate that these chemicals are weak developmental toxicants capable of producing mild fetotoxic effects in these species. Fetotoxicity was also indicated by effects on pup body weight and, for m-cresol, survival at parenterally toxic doses in two-generation reproduction studies in rats. Based on these data, it is not likely that cresols pose a serious developmental hazard to humans; however, the fact that they produce some effects on the developing fetus in animals suggests that care, should be taken to limit exposure in pregnant women.

Reproductive Effects. No reproductive effects have been reported in humans exposed to cresols. Although several studies in animals, including two-generation studies in rats and mink, examined the reproductive effects of cresols, no such effects were seen even at parenterally toxic doses. These results suggest that cresols do not have reproductive effects in animals or humans.

Genotoxic Effects. The genotoxic effects of cresols have been well studied. Genotoxicity assays on o-cresol are shown in Table 2-3a. Positive results were reported only in assays for chromosomal aberrations (Hazleton Labs 1988a) and sister chromatid exchange (Litton Bionetics 1981) in Chinese hamster ovary cells. The positive response in the assay for sister chromatid exchange is in contrast to negative results for sister chromatid exchange in human fibroblasts in vitro and mouse bone marrow, alveolar macrophages, and regenerating liver cells in vivo (Cheng and Kligerman, 1984). Although there are some discrepancies in the data, these findings suggest that o-cresol may be clastogenic under certain circumstances. The results of genotoxicity assays on p-cresol are shown in Table 2-3b. As was the case for o-cresol, p-cresol produced chromosomal aberrations in Chinese ovary cells (Hazleton Labs 1988a), but did not produce sister chromatid exchange in in vitro or in vivo assays by Cheng and Kligerman (1984). p-Cresol also produced cell transformation in mouse BALB/C-3T3 cells (Hazleton Labs, 1988d) and a minor increase in DNA synthesis in human peripheral lymphocytes in vitro (Daugherty and Franks 1986). These results suggest p-cresol has broader genotoxic activity than was implicated for o-cresol. Table 2-3c shows the results of genotoxtcity testing of m-cresol. A weak positive result was reported for SV40 induction in Syrian hamster kidney cells (Moore and Coohill 1983), but all other test results were negative, indicating that m-cresol is probably not genotoxic. The apparent genotoxicity of o- and p-cresols is supported by the finding that a 1:1:1 mixture of the three cresol isomers was positive in tests

TABLE 2-3a. Genotoxicity of o-Cresol

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms (in vitro):				
Salmonella typhimurium on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 1981; Pool and Lin 1982
Eukaryotic organisms (in vitro):				
Mammalian cells:				
L5178Y mouse lymphoma cells	Forward mutation	-	-	Litton Bionetics 1981
Primary rat hepatocytes	Unscheduled DNA synthesis	No data	-	Litton Bionetics 1981
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Hazleton Labs 1988a
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Litton Bionetics 1981
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	-	-	Hazleton Labs 1988b; Litton Bionetics 1981
Eukaryotic organisms (in vivo):				
Drosophila melanogaster	Sex-linked recessive lethal	No data	-	Hazleton Labs 1989d
Mouse	Dominant lethal	No data	-	Hazleton Labs 1989a
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; + = positive result

TABLE 2-3b. Genotoxicity of p-Cresol

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms (in vitro):				
Salmonella typhimurium on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Pool and Lin 1982
Eukaryotic organisms (in vitro):				
Mammalian cells:				
L5178Y mouse lymphoma cells	Forward mutation	-	-	Hazleton Labs 1988c
Human peripheral lymphocytes	Semiconservative/repair DNA synthesis	No data	(+)	Daugherty and Franks 1986
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Hazleton Labs 1988a
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	No data	+	Hazleton Labs 1988d
Eukaryotic organisms (in vivo):				
Drosophila melanogaster	Sex-linked recessive lethal	No data	-	Hazleton Labs 1989e
Mouse	Dominant lethal	No data	-	Hazleton Labs 1989b
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; + = positive result; (+) = weakly positive

TABLE 2-3c. Genotoxicity of m-Cresol

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms (in vitro):				
Salmonella typhimurium on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al 1983; Pool and Lin 1982
Eukaryotic organisms (in vitro):				
Mammalian cells:				
Syrian hamster kidney cells	SV40 induction	No data	(+)	Moore and Coohill 1983
L5178Y mouse lymphoma cells	Forward mutation	-	-	Hazleton Labs 1988c
Freshly cultured rat hepatocytes	Unscheduled DNA synthesis	No data	-	Hazleton Labs 1988e
Chinese hamster ovary cells	Chromosomal aberrations	-	-	Hazleton Labs 1988a
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	-	-	Hazleton Labs 1988d, 1988f
Eukaryotic organisms (in vivo):				
Mouse	Chromosomal aberrations (bone marrow)	No data	-	Hazleton Labs 1989c
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; (+) = weakly positive

for forward mutation in mouse lymphoma cells, sister chromatid exchange in Chinese hamster ovary cells, and cell transformation in mouse BALB/C-3T3 cells (Table 2-3d) (Litton Bionetics 1980a). Although o- and p-cresols and a 1:l:l mixture of all three cresol isomers gave some indication of genotoxic activity in in vitro assays, all in vivo assays were negative, and it is uncertain if cresols pose a genotoxic hazard in humans or other mammals following natural
exposure.

Cancer. Studies found no relationship between endogenous p-cresol levels in the urine and the occurrence of large bowel cancer (Bone et al. 1976) or bladder cancer (Renwick et al. 1988) in humans. There are no data available regarding the carcinogenicity of exogenous cresols in humans. No cancer bioassays have been conducted in animals, but the results of a promotion study in mice suggested that cresols can be cancer promoters. Cresols have some ability to interact with mammalian DNA in vitro, but it is impossible to assess the potential hazard to humans without more information.

2.5 BIOMAREERS OF EEPOSDRE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cresols are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity

TABLE 2-3d. Genotoxicity of a 1:1:1 Mixture of o-, p-, and m-Cresol

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms (in vitro):				
Salmonella typhimurium on plates	Reverse mutation	-	-	Litton Bionetics 1980a
Eukaryotic organisms (in vitro):				
Mammalian cells:				
L5187Y mouse lymphoma cells	Forward mutation	+	(+)	Litton Bionetics 1980a
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Litton Bionetics 1980a
Mouse BALB/C-3T3 cells	Cell transformation	+	No data	Litton Bionetics 1980a

- = negative result; + = positive result; (+) = weakly positive

or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance-specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cresols are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Cresols

No biomarkers that implicate exposure to cresols have been identified in humans or animals. Cresols are formed from the commonly found amino acid tyrosine, and occur naturally in human and animal tissues, fluids, and urine. Cresols are also formed as minor metabolites of toluene, and an increased presence of cresol in the body could be due to exposure to this substance. Therefore, even the cresols themselves cannot be considered to be biomarkers of cresol exposure unless very high levels are found. There is some evidence that methemoglobinemia, reduced glutathione levels in red blood cells, and Heinz body formation are associated with oral exposure to cresols in humans (Chan et al. 1971; Cote et al. 1984), but these effects are too general and occur at too high doses to be useful as biomarkers of exposure to cresols.

2.5.2 Biomarkers Used to Characterize Effects Caused by Cresols

No biomarkers of effects caused by cresols have been identified in humans or animals. It may be possible to use methemoglobinemia and Heinz body formation, which precede hemolytic anemia in humans (Chan et al. 1971; Cote et al. 1984), as biomarkers for the hemolytic effects of cresols, although these changes may be too general and occur at too high doses to be useful for this purpose.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Cresols promote the development of skin papillomas in mice following initiation with DMBA (Boutwell and Bosch 1959). It is possible that they would also promote the development of tumors initiated by other chemicals. Although no evidence is available, it is likely that cresols would interact with phenol on the central nervous system to produce convulsions and coma (Deichmann and Witherup 1944), and on the red blood cells to produce methemoglobinemia (Chan et al. 1971). Cresols have an oxidizing effect on red blood cells (Chan et al. 1971), and it.is likely that these effects would be

enhanced in the presence of other oxidizing compounds (e.g., hydroquinone). Cresols may also offer protection from the effects of some chemicals; all three isomers acted antagonistically to reduce paralysis produced by a-tubocurarine in rat diaphragm-phrenic nerve preparations (Mogey and Young 1949).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Several populations that may have increased vulnerability to the effects of cresols have been identified, although no strong evidence exists for any of them. There is some evidence that individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have increased susceptibility to the hematological effects of cresols; the increase in methemoglobin formation and decrease in glutathione levels were more pronounced in blood taken from subjects with G6PD deficiency than in blood taken from normal subjects following exposure of the blood to a disinfectant containing 50% cresols in vitro (Ghan et al. 1971). Infants may represent another population that is unusually sensitive to the effects of cresols. This possibility was suggested by the death of a l-year-old baby dermally exposed to high levels of cresols. People with immune deficiencies (e.g., human immuno-deficiency virus (HIV) infection) might be unusually susceptible to the apparent cancer promotional effects of cresols. In addition, individuals with seizure disorders might be expected to be more vulnerable to the effects of cresols on the central nervous system, such as coma and convulsions, than other people.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cresols. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cresols. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

The mechanisms by which cresols produce toxic effects are unknown, and the toxicokinetics of these compounds are not well understood. Procedures that might decrease the toxicity of cresols present in the bloodstream have not been identified. Although supporting data were not located, it is possible that elimination of cresols from the blood would be enhanced by alkaline diuresis, which would increase the proportion of cresols existing in the ionized state, thereby reducing reabsorption of cresols by the kidney tubules.

Procedures that have been used to manage people exposed to cresols are available (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Janusz 1988). For ingestion exposure, water or milk should be given if the patient is alert and has an intact gag reflex, Activated charcoal and a cathartic can then be administered orally or by gastric tube. Because cresol

is corrosive and may cause seizures, emesis should not be induced. If the eyes have been exposed, they should be thoroughly irrigated as soon as possible with running water or saline. If the skin has been exposed, it should be flushed promptly with copious amounts of water followed by thorough washing with soap or mild detergent and water.

Exposed individuals with evidence of central nervous system depression or seizures should be evaluated for the presence of some other underlying disorder. Diazepam or phenobarbital may be administered to alleviate seizures. Supplemental oxygen can also be administered. If pulmonary edema occurs, conventional therapy should be considered. Additional information regarding the treatment of individuals exposed to cresols may be obtained from Bronstein and Currance (1988), Haddad and Winchester (1990), and Stutz and Janusz (1988).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cresols is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cresols.

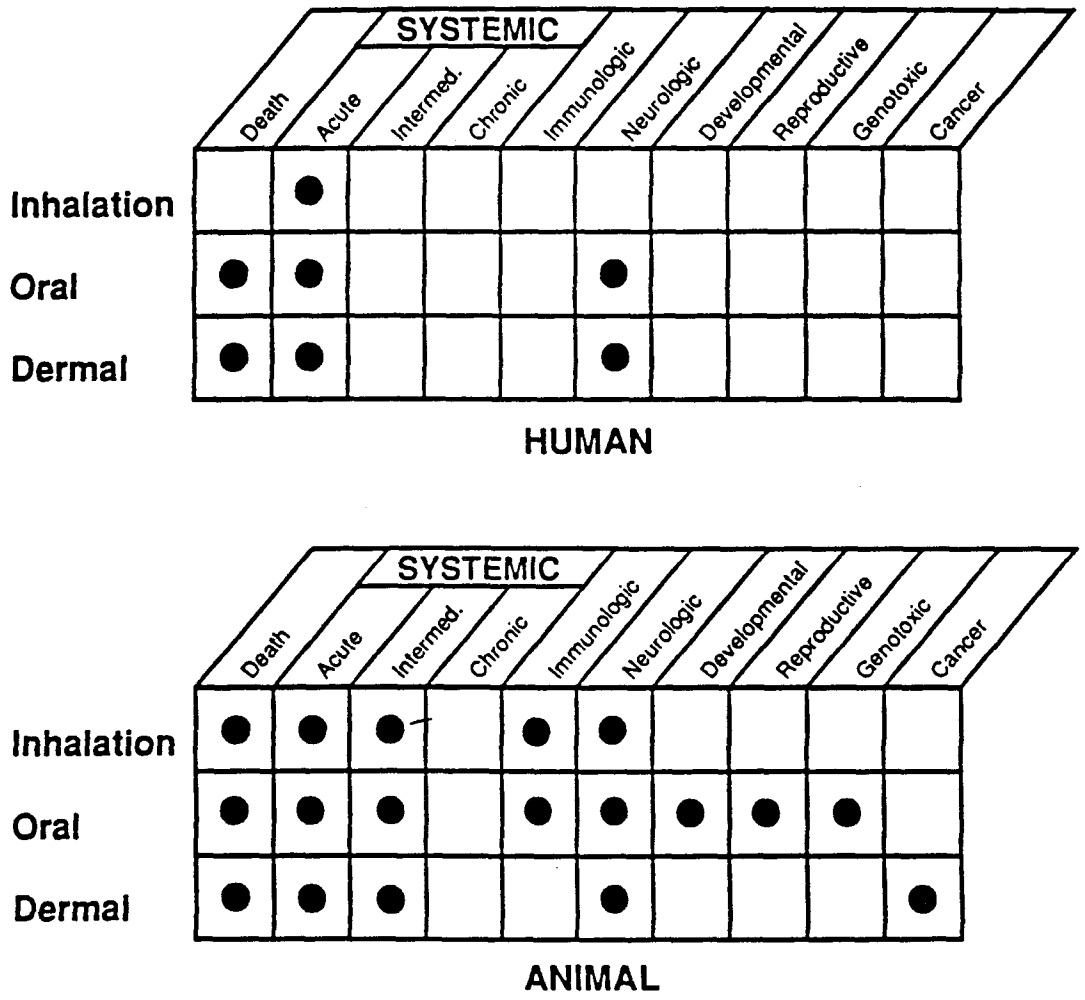
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Cresols

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cresols are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of cresols. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

In the following discussion, the various forms of cresol are considered together, due to the similarity of their effects and the levels at which these effects occur.

FIGURE 2-2. Existing Information on Health Effects of Cresols



The existing information on the health effects of cresols in humans comes almost entirely from case reports of people who either swallowed cresol-containing substances or had these substances spilled on them. The single exception was an inhalation study of mucosal irritation in humans.

A small number of studies investigated the effects of cresol inhalation in animals. These were acute- and intermediate-duration studies that either tried to determine lethal levels or looked at systemic and neurologic end points. One study included measurement of an end point relevant to immunotoxicity. Many studies of acute oral exposure were conducted in animals, mostly to determine lethal levels, but they include observations of systemic and neurologic effects. A recently completed series of intermediate-duration studies investigated the systemic and neurologic effects of each isomer in detail and also included immunologic and reproductive end points. Other oral studies included a series of detailed studies of the developmental effects of each isomer and two-generation reproduction studies. Studies of dermal exposure to cresols in animals generally looked at levels of lethality and irritation to the skin and eyes. One study of intermediate duration investigated dermal effects. A cancer-promotion study was also performed using dermally applied cresols.

2.9.2 Data Needs

Acute-Duration Exposure. Case reports of humans exposed to high doses of cresols, either orally or dermally, have provided acute toxicity information (Chan et al. 1971; Cote et al. 1974; Green 1975; Isaacs 1922; Jouglard et al. 1971; Klinger and Norton 1945; Labram and Gervais 1968; Larcan et al. 1974). The primary targets for cresol toxicity in humans appear to be the blood, kidneys, and nervous system. Lethal levels have been crudely estimated for both oral and dermal exposure. Animal studies of the acute toxicity of cresols have determined dose levels that produce skin irritation and death in dermally exposed animals, and reduced body weight, neurotoxicity, fetotoxicity, and death in orally exposed animals (BRRC 1988a, 1988b; MBA 1988a, 1988b, 1988c; TRL 1986, Vernot et al. 1977). Inhalation studies did not reliably identify target organs or hazardous levels, and pharmacokinetic data that might allow extrapolation from oral or dermal data are not available. Although the data were insufficient to derive inhalation MRLs, acute oral MRLs were calculated, based on maternal neurological effects in a developmental toxicity study (BRRC 1988b). Knowledge about the acute toxicity of cresols is important because people living near hazardous waste sites might be exposed to cresols for brief periods. Acute inhalation studies would enable determination of hazardous levels and identification of target organs for this route of exposure. Although case studies of exposed humans reported that the blood and kidneys are targets of cresol toxicity, acute effects on these organs have not been seen in animals. Careful study of these end points in acute animal studies would be appropriate. Acute oral and dermal studies that included gross and microscopic examination of all exposed animals would

provide better identification of possible target organs than necropsy of only the dead animals, as was done in existing studies. Examination of more subtle end points in these studies would also serve this purpose, and perhaps identify biomarkers of exposure and effects for cresols.

Intermediate-Duration Exposure. No information is available regarding humans exposed to cresols for an extended period of time. Oral studies of intermediate duration in animals have been performed for all three cresol isomers, and have helped to identify the levels at which cresols produce neurological, respiratory, hepatic, renal, hematological, and body weight changes in orally exposed animals (Homshaw et al. 1986; MBA 1988a, 1988b, 1988c; TRL 1986). Intermediate-duration studies by other routes of exposure were not located, and pharmacokinetic data that might allow extrapolation from oral data were not located. Additional oral studies might enable determination of intermediate MRLs. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods. Inhalation studies of intermediate duration would enable determination of hazardous levels and identification of target organs for this route of exposure, and might find effects that could not be detected in acute inhalation studies.

Chronic-Duration Exposure and Cancer. No studies of chronic duration were found in humans or animals. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to cresols for many years. Prolonged exposure to cresols in humans might occur by oral, inhalation, or dermal routes. Chronic studies would enable discovery of effects produced by long-term exposure to relatively low levels of cresols, which might not be detected in shorter-term studies.

No studies were located regarding the carcinogenicity of cresols in humans or animals. Cancer bioassays would be pertinent in light of results suggesting tumor-promoting potential following dermal application in mice (Boutwell and Bosch 1959) and positive results in some genotoxicity assays in mammalian cells in vitro (Hazleton Labs 1988a, 1988d; Litton Bionetics 1980a, 1981). Prolonged exposure to cresols in humans might occur by the oral, inhalation, or dermal routes, so cancer bioassays by any of these routes would provide useful information. Using known animal carcinogens to further study the promotional capabilities of cresols might also provide valuable information. For example, the potential of orally administered cresols to act as tumor promoters in the hamster forestomach, suggested by the results of Hirose et al. (1986), could be assessed.

Genotoxicity. No data were located regarding the genotoxicity of cresols in humans in vivo. In vitro studies using cultured human cells were negative for sister chromatid exchange for all three isomers (Cheng and Kligerman 1984) and positive for unscheduled DNA synthesis for p-cresol (Daugherty and Franks 1986). Studies of the genotoxicity of cresols in

animals in vivo reported only negative results (Cheng and Kligerman 1984; Hazleton Labs 1989a, 1989b, 1989c, 19898, 1989e). Results were mixed in in vitro studies using mammalian cells (Hazleton Labs 1988a, 1988b, 1988c, 1988d, 1988e, 1988f; Litton Bionetics 1980a, 1981), and uniformly negative in Salmonella assays (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 1981; Pool and Lin 1982). The positive results obtained in some human and animal in vitro tests suggest that cresols have some ability to react with DNA. More in vivo testing of cresols for genotoxic effects would enable better estimation of the actual genotoxic threat to humans posed by environmental exposure to these compounds.

Reproductive Toxicity. There are no data available regarding the reproductive effects of cresols in humans. Studies in animals, including two-generation studies in rats and mink (BRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986), developmental toxicity studies in rats and rabbits (BRRC 1988a, 1988b), and intermediate-duration toxicity studies in several species (Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c), found no evidence of reproductive toxicity. However, these studies were all performed using oral exposure. Since it is unknown how route of exposure affects the toxicokinetics of cresols, inhalation or dermal toxicity studies that included investigation of reproductive end points would provide further information about the potential reproductive hazard to humans posed by exposure to cresols. If positive results were obtained in these studies, multigeneration studies by these routes would be appropriate.

Developmental Toxicity. There are no data available regarding the developmental effects of cresols in humans. The developmental toxicity of cresols in animals was evaluated in a series of studies in which pregnant rats and rabbits were orally exposed to each cresol isomer (BRRC 1988a, 1988b, 1989a, 1989b, 1989c). These studies generally reported mild fetotoxicity at maternally toxic doses, which suggests that cresols are not developmental toxins in these species and may not pose a developmental hazard in humans. However, further testing of m-cresol, which produced effects on both parent and pup body weight at the low dose of a two-generation reproduction study (BRRC 1989c), would enable better assessment of the developmental toxicity of this isomer. It is unknown how route of exposure affects the toxicokinetics of cresols; therefore, studies using dermal or inhalation exposure would provide additional information about the potential developmental hazard to humans posed by exposure to cresols.

Immunotoxicity. No immunological effects were reported in case studies of human exposure. There was a decrease in spleen weight in rats orally exposed to p-cresol for 90 days (MBA 1988b), which, although unaccompanied by histopathological changes, suggests the possibility that cresols may affect the immune system. A battery of immune function tests would better enable assessment of the immunotoxicity of cresols in humans and animals.

Neurotoxicity. Exposure to cresols can produce facial paralysis and coma in humans (Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968). Effects leading up to coma have been identified in animal studies, and include hypoactivity, ataxia, and convulsions (BRRC 1988a, 1988b; MBA 1988a, 1988b, 1988c; TRL 1986). These effects are seen regardless of test species or route of exposure, and the levels at which these gross effects occur have been roughly identified. Acute MRLs were based on neurological effects in pregnant rabbits (BRRC 1988b). A few studies have included histopathological examination of nervous tissues, and one reported the occurrence of lesions, although exposure levels were not reported reliably (Uzhdavini et al. 1972). A detailed study of neurological effects reported clinical signs of neurotoxicity, but did not identify many significant differences between treated rats and controls in behavioral tests (TRL 1986). Two studies looked for, and found, subtle biochemical and neurophysiological changes in the brain(Mattsson et al. 1989; Savolainen 1979). Neurophysiological and neurochemical studies designed to assess the effects of cresol exposure would provide a much finer level of detail about the neurological effects of cresols than is currently known, and might identify the mechanism by which these effects occur.

Epidemiological and Human Dosimetry Studies. Epidemiology studies reported no relationship between urinary levels of endogenous p-cresol and bladder and bowel cancer (Bone et al. 1976; Renwick et al. 1988). No other epidemiological or human dosimetry studies regarding cresols were located. Epidemiological studies of exogenous cresol exposure would be useful to determine the effects of long-term exposure on humans, with particular attention paid to neurological effects. Although many people may be exposed to low cresol levels in the air or water, a study that focused on people exposed to higher levels, such as employees of industries that produce or use large amounts of cresol-containing substances, might provide more information because of the greater ability to detect a dose-response relationship between exposure and manifest disease. If a specific cause/effect relationship were established between cresol exposure and health effects in humans, monitoring of individuals living near hazardous waste sites could be performed in order to determine if exposure levels exceeded recommended limits and if body tissue and fluid levels of cresols and metabolites exceeded potentially hazardous levels.

Biomarkers of Exposure and Effect. No biomarkers of exposure to cresols have been identified. In fact, even the cresols themselves cannot be considered specific biomarkers for cresol exposure because they are also formed as breakdown products of toluene and tyrosine. However, if toluene exposure could be ruled out, then a high level of cresols or metabolites in the blood or urine would strongly suggest cresol exposure. Distinguishing biomarkers of exposure to cresols would enable early detection of cresol exposure and provide the opportunity for early treatment. One possibility

that can be further investigated is Heinz body formation in the blood of exposed humans (Chan et al. 1971; Cote et al. 1984).

No biomarkers of effect have been identified for cresols. Studies designed to investigate subtle effects might discern these biomarkers, which would enable finer delineation of the dose-response relationship for an effect and allow better estimation of the levels of cresols to which people could be exposed without risk. Case reports in humans have reported methemoglobinemia and Heinz body formation that may be predictive of hemolytic anemia (Ghan et al. 1971; Cote et al. 1984).

Absorption, Distribution, Metabolism, and Excretion. Levels of cresols in blood were obtained from a single case report of a dermally exposed human (Green 1975). Data on the toxicokinetics of cresols in animals were contained in two acute oral studies that provided only limited quantitative information on the absorption, metabolism, and excretion of cresols (Bray et al. 1950; Williams 1938). A more complete oral toxicokinetics study, in addition to studies using dermal and inhalation exposure, would provide data that could be used to develop predictive pharmacokinetic models for cresols. Inclusion of several dose levels and exposure durations in these studies would provide a more complete picture of the toxicokinetics of cresols and allow a more accurate route by route comparison, because it would allow detection of saturation effects. Studies of the tissue distribution of cresols in the body might help identify possible target organs.

Comparative Toxicokinetics. The nervous system is a target of cresols in both humans and animals. The blood and kidneys also appear to be targets in humans, although they have not clearly been identified as targets in animal studies using rats, rabbits, mink, or ferrets. The failure to detect these effects in animals could be related to differences in either dose received or toxicokinetics. No information is available regarding the toxicokinetics of cresols in humans; the two available toxicokinetic studies on cresols were both performed using rabbits (Bray et al. 1950; Williams 1938). Toxicokinetic studies in more species and using current techniques would result in either greater confidence on extrapolating the results to humans, if the results were similar in the species studied, or in extra caution about extrapolating to humans, if the results varied widely between species. As noted, variation in interspecies toxicokinetic parameters could also explain possible species differences in susceptibility to cresols.

Mitigation of Effects. Few data are available concerning the mechanism of action of cresols or the toxicokinetics of these compounds. Additional studies might identify specific steps that can be taken to alter the mechanism of action or the toxicokinetics of cresols so that the chance to interact with target organs is reduced. For example, knowledge of the influence of urinary pH on clearance and biological half-life might be useful for determining ways of increasing elimination of cresols.

2.9.3 On-going Studies

The National Toxicology Program (NTP) is performing subchronic tests of cresol toxicity in which either o-cresol or mixed cresol isomers are given to rats and mice in the feed. In addition, studies of the effects of cresols on reproduction and fertility in mice are being performed by the NTP. The results of these studies are not yet available.